REMARKS/ARGUMENTS

Claims 1-17 are pending in this patent application. Claims 18-20 have been canceld.

Vagueness Rejections and Objections.

The specification has been objected to because the Examiner found Table 1 confusing and seeks clarification. Table 1 is a compendium of mtDNA sequences that appears in the map of mtDNA sequences entitled MITOMAP found at www.mitomap.org. This sequence map is widely used by those of ordinary skill in the art and shows the sequence with a brief name (e.g., MTOHR), the location of the sequences on the base map (e.g., 110-441), a further shorthand notation for the sequence (e.g., OH) and a brief comment about the function or description of that sequence (e.g., H-strand origin). The table merely provides an overview of commonly identified mtDNA sequences so that the deletions identified at pages 8-10 can be put in their context in terms of location, identification, and description. That is, one can readily identify where the deletion occurs and what it affects. Because the notation and form of the table are commonly accepted by those of ordinary skill in the art Applicant respectfully requests the objection to this table be removed.

The Examiner's suggested changes in (b) and (c) of page 3 of the Office Action have been implemented with the amendments to the specification above.

Applicant respectfully requests that "Seq. ID. No" and "Seq. ID" in pages 31-39 and 41 be changed to "SEQ ID NO" by Examiner's amendment.

Claim objections have been overcome by the amendments to claims 8, 12, and 15.

Claims 1 and 4 have been rejected as anticipated by Todd. This rejection is respectfully traversed for the following reasons.

The claims have been amended so that it is clear that the nucleic acid amplified to detect mutations is mitochondrial DNA and the mutations are deletions that are least 4kb in length. Support for these amendments is found at page 7, line 30 and page 5, line 14. Accordingly, no new matter is introduced.

The Todd reference is not directed to mtDNA mutations nor are the mutations described and exemplified the large deletions of the instant inventions. Nowhere does the Todd reference recite mutations greater than a few base pairs. Indeed, point mutations are most notably represented. See e.g., page 15, line 9. The primers of the instant invention (mutant PCR primers described at page 7, line 21) would not be seen in this reference since they are primers that would hybridize sites on complementary sequences no less than 1 kb apart for wtDNA. Furthermore, while the Examiner has characterized the Todd reference as employing short PCR conditions, they are not those of the instant specification. This is seen by comparing the PCR conditions of the instant invention described at page 25 with those of Todd at, for example, page 16, line 4 (cyles of less than 1 minute versus those of 1 minute during the annealing/extension step). Accordingly, the instant invention is not anticipated by the Todd reference and this rejection is overcome.

Claims 1-3, 13, 15, and 16 have been rejected as anticipated by the Hernstadt reference. This rejection is respectfully traversed for the following reasons.

Hernstadt makes no mention of detecting the large deletions of mtDNA of the instant invention. The entire patent is directed to detecting mutations that manifest themselves in Alzheimer's disease and diabetes. Col. 2, lines 3 and 15. See also, Col. 6, line 7. All mutations described by Hernstadt are all small mutations effecting one or a few codons. There is no description of the large deletions or their detections as described and claimed in the instant invention. The primers of the instant invention (mutant PCR primers described at page 7, line 21) would not be seen in this reference since they are primers that would hybridize sites on complementary sequences no less than 1 kb apart for wtDNA. According, the instant invention is not anticipated by the Herstadt reference and this rejection is overcome.

Claims 5, 7, 9, 11, and 14 have been rejected as obvious over Hernstadt in combination with Todd. This rejection is respectfully traversed for the following reasons as are any other rejections involving this combination of references.

In order for references to be combined one or each of them must suggest their combination or provide motivation for doing so. Neither reference provides such a suggestion or motivation. The Todd reference describes the use of various restriction enzymes in the practice of PCR but makes no mention of mtDNA. The Hernstadt reference is directed to detecting mtDNA mutations but this arises from proper selection of mtDNA extraction processes in combination with proper primer selection only. See, e.g., Col. 7, line 15.

Even if one combined the references in the manner proposed by the Examiner one would not arrive at the instant invention. As described above, the references describe detection of relatively small mutations. Neither of them describes, suggests, or motivates one to use the mutant PCR primers of the instant invention to detect large deletions of mtDNA (e.g., those greater than or equal to 4kb). The very fact that the mutations described are in entirely different areas than those exemplified in the instant specification indicates that there was no such consideration by the inventors of the references. Todd, it will be recalled, is directed largely to RAS mutation, Hernstadt to AD and diabetes, the instant invention is directed largely to detecting large deletions associated with cardiac dysfunction. Page 2, line 23.

Because there is no suggestion or motivation to combine the references in the manner proposed by the Examiner and because their combination would not result in the instant invention is any event, this rejection is overcome.

Claims 6, 8, 10, 12, and 17 have been rejected as obvious over Hernstadt, Todd, and the Clinical Chemistry reference (Whitcome). This rejection is respectfully traversed for the same reasons as those set forth immediately above. Each of these claims contains the same limitations to mtDNA, deletion size, and mutant PCR

primers. As described above, no combination of the Hernstadt and Todd reference is warranted nor would any result in a method, article, or apparatus that would include these elements. Whitcome is cited for the proposition that inclusion of various probes in PCR processes. Accordingly, even if combinable with the other two references it does not detract from the patentability of the instant invention. This rejection is therefore overcome and a notice of allowance is respectfully solicited.

Respectfully submitted,

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